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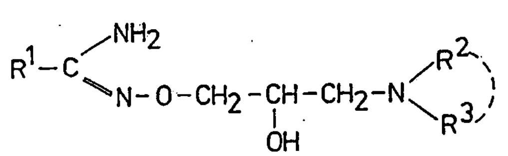
(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF AMIDOXIME DERIVATIVES



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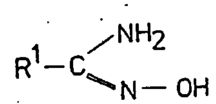

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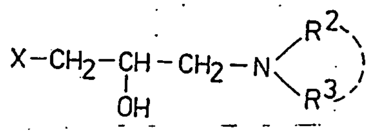

(III)

(57) Abstract

The invention relates to an improved process for preparing amidoxime derivatives of general formula (I), wherein R^1 means a C_{2-15} group, which may be unsaturated and/or cyclic alkyl, aralkyl group or optionally substituted and/or condensed aromatic and/or heteroaromatic group; R^2 stands for hydrogen or an optionally substituted straight or branched chain or cyclic and/or unsaturated C_{1-7} alkyl or aromatic group; R^3 represents an optionally substituted straight or branched chain or cylic and/or unsaturated C_{1-7} alkyl or aromatic group; or R^2 and R^3 together with the adjacent nitrogen atom may form a 5- to 8-membered ring optionally containing other heteroatom(s); and X stands for halogen and their salts by reacting an amidoxime of general formula (II), wherein R^1 is as defined above, in the presence of an alkaline substance, transforming the product to a salt with an acid or transforming the salt to the base, which comprises reacting the amidoxime with an alkaline metal hydroxide or alkaline metal alkoxide and dimethylformamide or 1,3-dimethyl-2-imidazolidinone, preferably in the presence of a proton source, reacting the amidoxime complex thus obtained preferably without isolation with an amine of general formula (III). The invention relates further to pure O-(2-hydroxy-piperidino-1-propil)nicotinic acid amidoxime hydrochloride and hydrobromide and O-(2-hydroxy-3-piperidino-1-propyl)nicotinic acid amidoxime base.

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IMPROVED PROCESS FOR THE PREPARATION OF AMIDOXIME DERIVATIVES

This invention relates to an improved process for preparing amidoxime derivatives.

In the general formulae used herein, the meaning of the substituents is throughout as follows if not indicated otherwise:

R^1 means a C_{2-15} group, which maz be unsaturated and/or cyclic alkyl, aralkyl group or optionally substituted and/or condensed aromatic and/or heteroaromatic group;

R^2 stands for hydrogen or an optionally substituted straight or branched chain or cyclic and/or unsaturated C_{1-7} alkyl or aromatic group;

R^3 represents an optionally substituted straight or branched chain or cyclic and/or unsaturated C_{1-7} alkyl or aromatic group; or

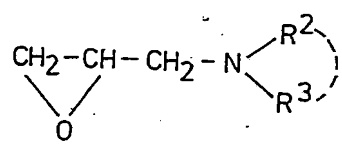
R^2 and R^3 together with the adjacent nitrogen atom may form an 5- to 8-membered ring optionally containing other heteroatom(s); and

X stands for halogen.

It is known that several representatives of amidoxime derivatives of the general formula (I) are useful for the treatment of diabetic angiopathy which is practically unique up to the present. Other amidoxime derivatives show a blood pressure lowering action, too and eventually, an alpha--blocking effect may also be observed (British patent specification No. 1,582,029; United States patent specifications Nos. 4,187,220 and 4,308,399). The possibility of the use of these compounds as therapeutic drugs demands an economical preparation which can be carried out on an industrial scale, too.

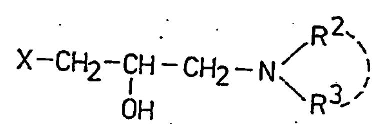
It is known that O-substitued derivatives of oximes are usually prepared by employing alkylating agents /Houben Weyl Vol. X/4, pages 217 to 220 (1968)/. The O-substituted

amidoximes according to the present invention have been prepared by reacting amidoximes with epoxides (or their functional equivalents), i.e. with the epoxy compounds of the general formula (IV)



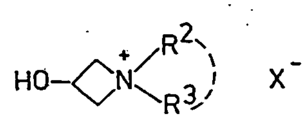
(IV)

or with 1-halo-2-hydroxy-3-propanamines of the general formula (III)



(III)

or with 3-hydroxyazetidine salts of the general formula (V)

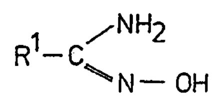


(V)

respectively. Protic solvents such as water, methanol, ethanol or mixtures of water with a water-immiscible solvent, e.g. benzene were used as solvents in these reactions. The final products were isolated by extraction (eventually after evaporation), the extract was washed

several times with a concentrated alkaline solution and after solvent change it was acidified by alcoholic hydrochloric acid and carefully crystallized. The hydrochlorides of the products were obtained in yields between 6% and 50% in this way.

On reproduction and scale increase of these reactions it has surprisingly been found that the amidoximes of the general formula (II)

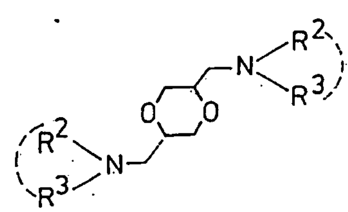


(II)

could not completely be transformed. After a reaction of about 60 to 70%, the reaction stopped and both an increase in the reaction temperature or use of an excess of reactant enhanced the amount of tarry side products which inhibited the isolation of the product.

Thus, the aim of the present invention is to provide an industrial plant process which is free from the above disadvantages.

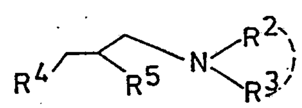
It is known from the literature /J. Am. Chem. Soc. 80,1257 (1958); Appl. Polym. Sci. 11, 145-8 (1967); and J. Chem. Soc. 1950, 2257-2272/ that amines of the general formula (III) are unstable: on standing they are reversibly transformed to a cyclic salt of the general formula (V) or dimerize to a dioxane derivative of the general formula (VI)



(VI)

Concerning the synthesis, the former transformation does not mean any drawback since amidoximes can be reacted with salts of the general formula (V) in the presence of a base. However, the latter transformation is irreversible which can cause a significant substance loss in the synthesis.

One basis of the present invention consists in the recognition that the compounds of the general formulae (III), (IV) or (V), respectively, react also with water, alcohols and acids to give side products of the general formula (IX)

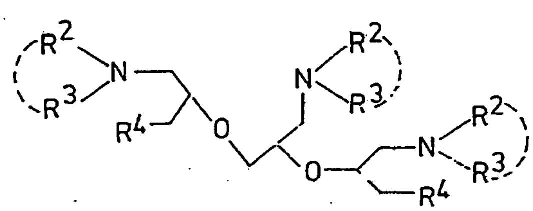


(IX)

wherein

R^4 and R^5 stand for hydroxyl, C_{1-4} alkoxy, C_{2-8} alkanoyl or acid residue.

Depending from the dimensions of the R^4 and R^5 groups, particularly in the case of a hydroxyl or lower alkoxy group, a polymerization of significant extent can also occur which can lead e.g. to compounds of the general formula (XI)



(XI)

The present invention is based on the other recognition that the appearance of these decomposition products is responsible for "stopping" of the coupling reaction. The appearance of the decomposition products is presumably favourable for SN1 reactions and therefore results in a protic system promoting a further decomposition and inhibiting the reaction of amidoxime. It has been stated by using model reactions that the reactants of the general formulae (III), (IV) and (V) are very unstable under the conditions described up to the present and the side reactions are promoted either by basic or acidic catalysis. Thus, in the case of the epoxide of general formula (IV) the basic catalysis favours a terminal substitution whereas an acid catalysis promotes the substitution on the C-2 carbon atom. In the coupling reaction with the amidoxime, the epoxide of the general formula (IV) is completely decomposed within 2 to 4 hours.

Based on the above recognitions it was first above all aimed to find a reaction medium or reaction conditions, respectively , wherein the reactants are not decomposed and the selective coupling of the amidoxime of general formula (II) and formation of the final product are promoted and accelerated either by suppressing the formation of contaminants recognized by us or by separating the final product from these contaminants eventually formed in little amounts.

Thus, the present invention relates to a process for the preparation of amidoximes of the general formula (I) by reacting an amidoxime of the general formula (II) with an amine of the general formula (II) with an amine of the general formula (III) and/or (IV) in the presence of a basic substance, which comprises reacting the amidoxime with an alkaline metal hydroxide or alkaline metal alkoxide and dimethylformamide or 1,3-dimethyl-2-imidazolidinone,

preferably in the presence of a proton source, reacting the amidoxime complex thus obtained preferably without isolation with an amine of the general formulae (III) and/or (IV) and/or (V) under SN2 reaction conditions at a temperature between 0 ^{o}C and 100 ^{o}C, suitably in the presence of a metal salt catalyst then, if desired, selectively separating the thus formed product of general formula (I) from the side products and/or converting it with acids to salts, if desired, to mixed salts and crystallizing it or, if desired, converting it to base and/or again transforming it to a salt by using an other acid.

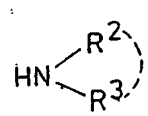
According to a preferred embodiment of the process of the invention, the reactants of the general formulae (III), (IV) and (V) are used in an excess of 0.05 to 0.15 equivalent and optionally a catalyst is employed.

It is suitable to use dimethylformamide (DMF) or N,N--dimethyl-2-imidazolidinone (DMI) with a water content of 1% or less which are free from contaminations arising e.g. from a decomposition since otherwise the yield may be deteriorated or an undesired transformation of DMF or DMI may be induced.

The formation and aimed preparation, respectively, of the complex are substantial factors of the present invention. A very significant amount of precipitate was observed in a reaction carried out in dimethylformamide at 50^{o}C by using an alkaline hydroxide as base. This precipitate gradually disappeared as the reaction proceeded.For the preparation of the complex, it is not necessary to separate it from the mixture. For improving the solubility conditions and ensuring the proton transfer it is preferred to add a proton source, preferably tertiary butanol to the mixture whereby the yield is increased by 3 to 5% and the reaction time is shortened. The complex is reacted further preferably at 30 to 75 ^{o}C.

It has been stated that the purity of the starting amines of general formulae (III), (IV) or (V), respectively, is important for the course of the reaction. All these three compounds can excellently be reacted in a pure state whereas the purification and storage of these reactants can be solved only with difficulties on an industrial scale even because of their high reactivity. Therefore a simple method of preparing these products was developed in order to achieve an easy connection with the solution of the present invention.

It has been found that it is suitable to react the amidoxime complex prepared according to the present invention with an amine of the general formulae (III), (IV) or (V), respectively, which has been prepared by reacting epichlorohydrin with an amine of the general formula (VII)



(VII)

in the presence of tertiary butanol taken in a ratio of 1:0.8 to 1:1.2 calculated for the mass of the amine.

Preferably, the amines of the formulae (III), (IV) or (V) are reacted with the complex according to claim 1 without isolation from the reaction mixture after their preparation by using dimetylformamide as further solvent. In this way, the amidoxime derivative of the general formula (I) can be prepared in a good yield in the same equipment (in "one-pot" reaction).

However, the reaction lasts for a longer time owing to the inhibiting effect of the decomposition products

discussed above. In these cases the use of the catalysts mentioned above is particularly preferred.

Thus, according to the present invention the preparation of the target compounds with a good efficacy has been solved simultaneously with the possible suppression of side reactions. However, as the product is accompanied by some amount of contaminating substances, the invention further relates to a selective separation of the final product from the accompanying undesired substances.

For the selective separation of the product the reaction mixture is optionally diluted with a solvent, neutralized by acid at 40 to 70 °C optionally after filtration then, optionally after a repeated filtration, the mixture is acidified, the salts and contaminations (optionally the catalyst) precipitated at a pH value of 4 to 5 at 50 °C or at a pH value of 2 to 3 at 70 °C are separated from the reaction mixture and subsequently, the salt formed from the amidoxime derivative of general formula (I) with an acid is crystallized by adjusting the pH of the reaction mixture to 1 to 3. Hydrochloric acid is preferably used for the acidification.

The process according to the invention is more simple than those known up to the present and the purity of the substances obtained as crude products is essentially higher. From the point of view of the operations, it is easy to increase to an industrial scale and to realize. The yields are excellent (75 to 97 %) and can further be improved by working up the mother liquors of crystallization. After evaporation and alkaline extraction of the mother liquor the solution can again be crystallized by acidification as described above.

By using the process according to the present invention it became successful to isolate in a pure crystalline state O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime

base, m.p.: 70-73 °C which has not been described up to the present. The most important physico-chemical characteristics of this substance are as follows.

IR spectrum (KBr): γ -O-C=N 1642 cm^{-1}

^{1}H-NMR spectrum ($CDCl_3$, δ ppm): 1.48 m, (6H), CH_2-piperidine; 2.42 m, (6H), $3xCH_2N$; 3.36, br, (1H), CH-O; 4.08 m, (3H), 1-CH_2, OH; 5.2, br, (2H), NH_2; 7.30 m (1H), pyridine-5'; 7.92 m, 4', 8,62 m (1H), 6', 8,88 m, (1H), 2'.

1 g of this substance dissolved in 10 ml of concentrated sulfuric acid gives a yellowish homogeneous solution.

The invention relates to this novel substance, too.

Similarly, it has been successful to obtain in a very pure state O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime hydrochloride and hydrobromide salts. The hydrobromide has not been described at all up to the present; the hydrochloride has been published only in an unsuitable purity. The spectroscopic characteristics of these new substances are as follows.

UV spectrum: λ_{max} 274.237 nm

IR spectrum (KBr): γ -O-C=N 1649 cm^{-1}

^{1}H-NMR spectrum (DMSO-d_6, δ ppm): 1.80, br, (6H), CH_2--piperidine; 2.65-3.75 m, (6H $3xCH_2$-N); 4.00 m, (2H), 1-CH_2; 4.40 m (1H), CH-O; 7.00, br, (4H), $2xNH^+$, NH_2; 8.00 dd, (1H), pyridine-5'; 8.75 m, (1H), 4'; 8.95 m, (1H), 6'; 9.13 d, (1H), 2'; 10.35, br, (1H), OH.

1 g dissolved in 10 ml of concentrated sulfuric acid gives a yellowish homogeneous solution.

The process of the invention is illustrated in detail by the following non limiting Examples.

Example 1

1.0 g (25 mmol) of powdered sodium hydroxide and 4.7 ml (50 mmol) of tert-butanol are added to the solution of 6.9 g

(50 mmol) of nicotinic acid amidoxime in 50 ml of pure dry DMF. To the resulting suspension 7.8 g (55 mmol) of redistilled N-(2,3-epoxypropyl)piridine /J. Am. Chem. Soc. 80 1257-9 (1958)/ are added at 50 °C and stirred at 70 °C. The course of the reaction is observed by thin layer chromatography (TLC). After complete termination of the reaction the pH of the solution is adjusted to 6 and after clarifying and filtering it the filtrate is acidified to pH 2.5 and crystallized. The pale yellow crystalline precipitate is filtered to give O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime dihydrochloride in 16.5 g (94 %) yield, m.p.: 202-204 °C after recrystallization from ethanol. The first generation is 14.9 g of pale yellow product which is of 99.1 % purity based on displacement method or on the determination of Cl^- and 99.2 % based on spectrophotometric and nitrogen determination, m.p.: 202-204 °C. The yield is 85 %.

UV spectrum: λ_{max} 274.237 nm

IR spectrum (KBr): ν -O-C=N 1649 cm^{-1}

^{1}H-NMR spectrum (DMSO-d_6, δ ppm): 1.80, br, (6H), CH_2-piperidine; 2.65-375 m, (6H, 3xCH_2-N); 4.00 m, (2H), 1-CH_2; 4.40 m, (1H), CH—O; 7.00, br, (4H) 2xNH^+, NH_2; 8.00 dd, (1H), pyridine-5'; 8.75 m, (1H), 4'; 8.95 m, (1H), 6'; 9.13 d, (1H), 2'; 10,35, br. (1H), OH.

1 g of the product dissolved in 10 ml of concentrated sulfuric acid gives a yellowish homogeneous solution.

Example 2

435 ml of dry tert-butanol and 676 g (4.785 mol) of N-(2,3-epoxypropyl)piperidine are added to the mixture containing 596 g (4.35 mol) of nicotinic acid amidoxim, 4350 ml of pure dry DMF and 100 g (2.5 mol) of sodium hydroxide. The pale brown suspension is stirred at 65 °C for 3 hours. The course of the reaction is observed as described in Example 1. After acidifying the mixture to pH=6 it is

clarified, filtered and the dark yellow solution is adjusted to pH 2.5. The pale yellow crystalline precipitate is filtered to give 1480 g of O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime dihydrochloride in a purity of 95 %. The yield is 92 %. After recrystallization the total yield together with the second and third generations amounts to 88 % calculated for the starting substances. The purity of the crystallized product is 99.5 %, m.p.; 202-204 °C. The product is identical to that of Example 1.

Example 3

After mixing 41.3 g of nicotinic acid amidoxime, 750 ml of dry DMF and 6 g of NaOH, 46.6 g of N-(2,3-epoxypropyl)piperidine are added to the complex obtained and the mixture is reacted at 65 °C for 4 hours. Meantime the orange red thick suspension is transformed to a pale brown solution corresponding to the course of the reaction. After distilling off 400 ml of DMF from the solution during 90 minutes the mixture is cooled to room temperature and diluted with 500 ml of dry isopropanol. After adjusting the pH of the solution to 6 to 7 and then filtering off the contaminations, the pH of the pale yellow solution is adjusted to 2.5 by adding hydrochloric acid and left to slowly crystallize. 81 g of butter-coloured crystalline hydrochloride are obtained, m.p.: 202-205 °C. This product is analytically identical to those described in the preceeding Examples. From the mother liquior 14.5 g of pale yellow crystalline product are obtained as 2nd generation, m.p.: 195-200 °C. The total yield amounts to 90.6 %.

Example 4

By treating O-(2-hydroxy-3-piperidino-1--propyl)nicotinic acid amidoxime dihydrochloride with sodium hydroxide solution the base is obtained and as a white crystalline substance O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime is isolated in a pure state, m.p.:

70-73 °C.

IR spectrum (KBr): γ -O-C=N- 1642 cm^{-1}

^{1}H-NMR spectrum ($CDCl_3$, δ ppm): 1,46 m, (6H), CH_2-piperidine; 2,42 m, (6H), $3xCH_2N$; 3,36, br, (1H), OH-O; 4,06 m, (3H), 1-CH_2, OH; 5,2 br, (2H), NH_2; 7,30 m, (1H), piridine 5'; 7,92 m, (1H), 4'; 8,62 m, (1H), 6'; 8,88 m, (1H), 2'.

1 g of this substance dissolved in 10 ml of concentrated, sulfuric acid gives a yellowish homogeneous solution.

Example 5

O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime is prepared as described in Example 1, except that the acidification is carried out by an ethanolic solution of dry hydrogen bromide to obtain 20.5 g of O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime dihydrobromide in a yield of 93 % (together with the 2nd generation), m.p.: 180-184 °C.

Example 6

The process described in Example 1 is followed, except that the salt is formed by using an isopropanolic solution saturated by dry hydrogen chloride (with a concentration of about 8.5 mmol/ml) to give O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime dihydrochloride in a yield of 95 %.

Example 7

The process described in Example 1 is followed, except that no tert-butanol is used. The reaction mixture is stirred for 6 hours at 70 °C to give a total yield of 94 %.

Example 8

The process described in Example 1 is followed, except that no tert-butanol is used and 1.12 g (10 mmol) of potassium tert-butoxide are employed as base. After stirring the reaction mixutre at 70 °C for 3 hours a total yield of 16.67 g (95 %) is obtained.

Example 9

The process described in Example 1 is followed, except that 70 ml of DMF, 5.0 g (125 mmol) of sodium hydroxide are used and as reactant 11.8 g (55 mol) of 1-chloro-2-hydroxy-3-piperidinopropane hydrochloride (Monatshefte für Chemie, 15, 119) are added. After stirring the reaction mixture at 70 °C for 6 hours the product is obtained in a total yield of 16.7 g (95 %).

Example 10

The process described in Example 1 is followed, except that 3.2 g (80 mmol) of powdered sodium hydroxide, 7.5 ml of tert-butanol are used and as reactant 9.8 g (55 mmol) of 1,1-pentamethylene-3-hydroxyazetidinium chloride (J. Org. Chem. 33 (2) 523) are added. After stirring the suspension at 70 °C for 3 hours O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime dihydrochloride is obtained in a total yield of 15.8 g (90 %).

Example 11

The process described in Example 1 is followed, except that 1.0 g (10 mmol) of aluminum oxide is used as catalyst. After recrystallization the product is obtained in a yield of 14.9 g (85 %), m.p.: 206-209 °C.

Example 12

The process described in Example 1 is followed, except that 1.5 g (10 mmol) of stannic oxide are used as catalyst. After recrystallization the product is obtained in a yield of 14.7 g (84 %), m.p. 207-210 °C.

Example 14

The process described in Example 1 is followed, except that 9.3 g (50 mmol) of 2-amino-5-chlorobenzamidoxime are used as acid amidoxime component and after acidification the reaction mixture is evaporated under reduced pressure. The thick oily residue is dissolved in 50 ml of hot isopropanol and left to crystallize to give a yield of 15.0 g, m.p.: 189-190 °C.

Example 15

4.7 g (5.5 ml; 55 mmol) of piperidine are added during 20 minutes to the solution of 5.1 g (4.3 ml; 55 mmol) of epichlorohydrin in 5.2 ml of tert-butanol under cooling by water while stirring vigorously. The reaction mixture is stirred at room temperature for 1 hour, then 50 ml of pure dry DMF, 6.9 g (50 mmol) of nicotinic acid amidoxime and 3.2 g (80 mmol) of powdered sodium hydroxide are added. After stirring the suspension at 70 °C for 12 hours the reaction mixture is worked up as described in Example 1 to give 13.2 g (75 %) of O-(3-amino-2-hydroxypropyl) nicotinic acid amidoxime dihydrochloride.

Examples 16 to 26

General process for the preparation of O-alkylated acid amidoxime derivatives of the general formula (I).

Method A

50 mmol of an acid amidoxime of the general formula (II) are dissolved in 50 ml of pure dry DMF, then 25 mmol of a basic catalyst, 4.7 ml (50 mmol) of tert-butanol and finally 55 mmol of an 1-(2,3-epoxypropyl)amine of the general formula (IV) are added.

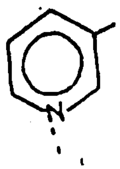
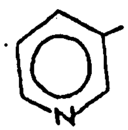
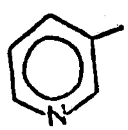
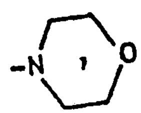
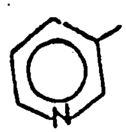
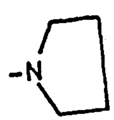
After stirring at 70 °C until complete termination of the reaction, the mixture is acidified as described in Example 1 and then the product of the general formula (I) is isolated.

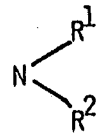
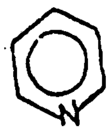
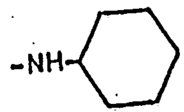
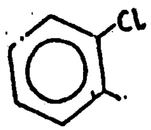
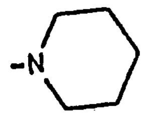
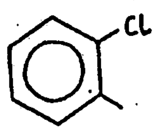
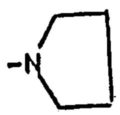
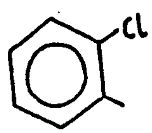
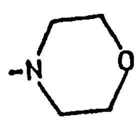
Method B

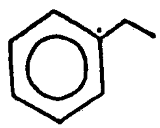
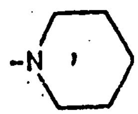
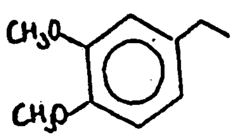
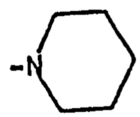
The process described under method A is followed, except that the reaction mixture is acidified and evaporated as described in Example 14 and the product obtained is crystallized from a solvent.

Method C

The process described under method A is followed, except that the free base is liberated as described in Example 4 and then is crystallized from a solvent or isolated as an oil.

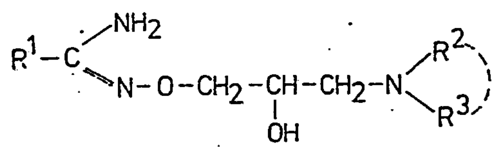
Example No.	R^1	$N{<}{R^1 \atop R^2}$	Time of reaction hour	Catalyst	Method	Isolated form	Crystallization solvent	m.p. °C
16		$-N{<}{C_2H_5 \atop C_2H_5}$	4	NaOH	B	HCl salt	Ethanol/ /izopropanol	78-81
17		$-N{<}{(CH_2)_3CH_3 \atop (CH_2)_3CH_3}$	13	NaOH	B	HCl salt	Acetonitrile	77-80
18		$-N{<}{(CH_2)_5CH_3 \atop (CH_2)_5CH_3}$	15	NaOH	B	HCl salt	Acetonitrile	110-116
19			8	NaOH	B	HCl salt	abs. Ethanol	92-99
20			15	NaOH			abs. Ethanol	175-177,5

Example No.	R^1		Time of reaction hour	Catalyst	Method	Isolated form	Crystallization solvent	m.p. °C
21			22	NaOH	C	Base	Diethyl ether	90-93
22			23	NaOH	A	HCl salt	DMF	219-221
23			18	NaOH	B	HCl salt	Izopropanol	204-212
24			8	NaOH	B	HCl salt	Acetonitril	157--162

Example No.	R^1	$N{<}{\substack{R^1\\R^2}}$	Time of reaction hour	Catalyst	Method	Isolated form	Crystallization solvent	m.p. °C
25			32	KOtBu	C	Base	Petrol-ether	94-97
26			23	KOtBu	B	HCl salt	DMF	202-203

Claims

1. A process for the preparation of amidoxime derivatives of the general formula (I), wherein



(I)

R^1 means a C_{2-15} group, which may be unsaturated and/or cyclic alkyl, aralkyl group or optionally substituted and/or condensed aromatic and/or heteroaromatic group;

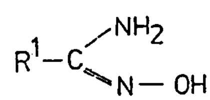
R^2 stands for hydrogen or an optionally substituted straight or branched chain or cyclic and/or unsaturated C_{1-7} alkyl or aromatic group;

R^3 represents an optionally substituted straight or branched chain or cyclic and/or unsaturated C_{1-7} alkyl or aromatic group; or

R^2 and R^3 together with the adjacent nitrogen atom may form an 5- to 8-membered ring optionally containing other heteroatom(s); and

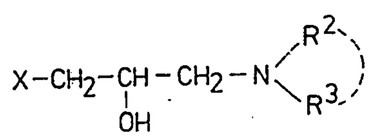
X stands for halogen

and their salts by reacting an amidoxime of the general formula (II),



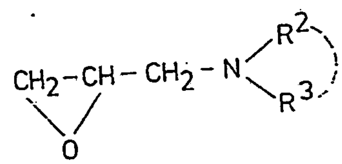
(II)

wherein R^1 is as defined above, in the presence of an alkaline substance, transforming the product to a salt with an acide or transforming the salt to the base, which comprises reacting the amidoxime with an alkaline metal hydroxide or alkaline metal alkoxide and dimethylformamide or 1,3-dimethyl-2-imidazolidinone, preferably in the presence of a proton source, reacting the amidoxime complex thus obtained preferably without isolation with an amine of the general formulae (III)



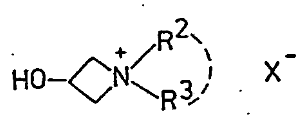
(III)

and/or (IV)



(IV)

and/or (V)



(V)

wherein R^2 and R^3 are as defined above under SN2 reaction conditions at a temperature between 0 °C and 100 °C, suitably in the presence of a metal salt catalyst then, if desired, selectively separating the thus formed product of general formula (I) from the side products and/or converting it with acids to salts, if desired, to mixed salts and crystalliying it or, if desired, converting it to base and/or again transforming it to salt by using an other acid.

2. The process as claimed in claim 1, which comprises using tertiary butanol as a proton source.

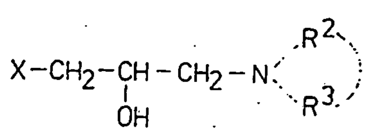
3. The process as claimed in claim 1 or 2, which comprises reacting the complex with the amine at a temperature between 30 °C and 75 °C.

4. The process as claimed in any of the claims 1 to 3 which comprises using aluminum oxide, tin oxide, dibutyltin oxide or their organic complexes as metal salt catalysts.

5. The process as claimed in any of the claims 1 to 4, which comprises for the selective separation of the product of general formula (I), wherein R^1, R^2 and R^3 are as defined above, optionally diluting the reaction mixture with a solvent, then neutralizing at 40 to 70 °C by acid optionally after filtration, then acidifying the mixture, separatir from the mixture the salts and contaminations precipitated at a pH value of 4 to 5 at 50 °C or at a pH value of 2 to 3 at 70 °C and crystallizing the salt formed with an acid of the amidoxime derivative of the general formula (I), wherein R^1, R^2 and R^3 are as defined above, by adjusting the pH value of the reaction mixture to 1 to 3.

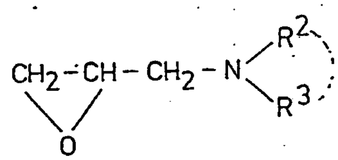
6. The process as claimed in claim 1 to 5, which comprises using hydrochloric acid for the acidification.

7. The process as claimed in claim 1, which comprises reacting an amidoxime complex prepared according to claim 1 with an amine of the general formula (III),



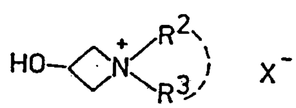
(III)

or of the general formula (IV)



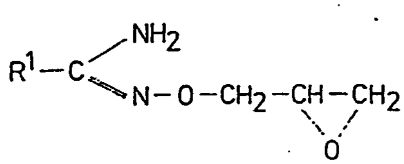
(IV)

or of the general formula (V)



(V)

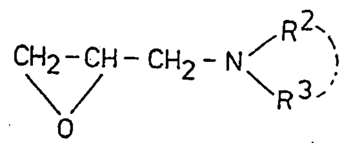
respectively, wherein R^2, R^3 and X are as defined above, which have been prepared by reacting epichlorohydrin with an amine of the general formula (VII)



(VII)

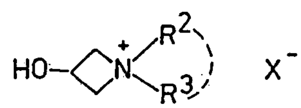
wherein R^2 and R^3 are as defined above, in the presence of tertiary butanol taken in an 1:0.8 to 1:1.2 ratio calculated

and/or (IV)



(IV)

and/or (V)



(V)

wherein R^2 and R^3 are as defined above under SN2 reaction conditions at a temperature between 0 °C and 100 °C, suitably in the presence of a metal salt catalyst then, if desired, selectively separating the thus formed product of general formula (I) from the side products and/or converting it with acids to salts, if desired, to mixed salts and crystalliying it or, if desired, converting it to base and/or again transforming it to salt by using an other acid.

for the mass of the amine.

8. The process as claimed in claim 7, which comprises reacting the amines of the general formulae (III), (IV) or (V), respectively wherein R^2, R^3 and X are as defined above, without isolation from the reaction mixture after their preparation, with the complex prepared according to claim 1 by using dimethylformamide as a further solvent.

9. Pure O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime hydrochloride and hydrobromide characterized by giving, when dissolved in an amount of 1 g in 10 ml of concentrated sulfuric acid, yellow homogeneous solution

UV spectrum: λ_{max} 274.237 nm

IR spectrum (KBr): ν-O-C=N 1649 cm^{-1}

^1H-NMR spectrum (DMSO-d_6, δ ppm): 1.80, br, (6H), CH_2-- piperidine; 2.65-3.75 m, (6H, $3xCH_2$-N); 4.00 m, (2H), 1-CH_2; 4.40 m (1H), CH-O; 7.00, br, (4H), $2xNH^+$, NH_2; 8.00 dd, (1H), pyridine-5'; 8.75 m, (1H), 4'; 8.95 m, (1H), 6'; 9.13 d, (1H), 2'; 10.35, br, (1H), OH.

10. Pure crystalline O-(2-hydroxy-3-piperidino-1-propyl) nicotinic acid amidoxime base characterized by a melting point of 70 to 73 ^oC, giving, when dissolved in an amount of 1 g in 10 ml of concentrated sulfuric acid, a yellow homogeneous solution and having the following spectroscopic characteristics:

IR spectrum (KBr): ν-O-C=N 1642 cm^{-1}

^1H-NMR spectrum ($CDCl_3$, δ ppm): 1.48 m, (6H), CH_2-piperidine; 2.42 m, (6H), $3xCH_2N$; 3.36, br, (1H), CH-O; 4.08 m, (3H), 1-CH_2, OH; 5.2, br, (2H), NH_2; 7.30 m (1H), pyridine-5'; 7.92 m, 4', 8,62 m (1H), 6', 8,88 m, (1H), 2'.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 90/00003

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^5: C 07 C 251/58, C 07 C 249/12, C 07 D 213/58, C 07 D 413/12, 401/12

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
$Int.Cl.^5$	C 07 C 249/00, C 07 C 251/00, C 07 D 213/00, C 07 D 401/00, C 07 D 403/00, C 07 D 413/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [*]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	GB, A, 1 582 029 (CHINOIN GYOGYSZER), 31 December 1980 (31.12.80), see claims 1,36-39,42.	(1,3,5-7)
A	US, A, 4 187 220 (KALMAN TAKACS et al.), 05 February 1980 (05.02.80), see abstract; column 2, line 57 - column 5, line 38.	(1,2,5-7)
A	US, A, 4 308 399 (KALMANTAKACS et al.), 29 December 1981 (29.12.81), see column 1, line 59 - column 5, line 45.	(1,2,5-7)
A	DE, A1, 3 620 166 (BAYER), 17 December 1987 (17.12.87), see abstract.	(1,7)
A	CH, A5, 634 828 (DUPHAR INTERNATIONAL), 28 February 1983 (28.02.83), see claims 1,4.	(1,7)
A	EP, A1, 0 023 560 (BASF), 11 February 1981 (11.02.81), see claim 1.	(1,7)
A	EP, A1, 0 121 701 (ALLIED CORPORATION), 17 October 1984 (17.10.84), see claims. ----	(1-3,7)

* Special categories of cited documents: [10]
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 March 1990 (05.03.90)	19 March 1990 (19.03.90)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

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		SE-B - 435280	17-09-84
		SE-C - 435280	20-12-84
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		AT-A - 415/77	15-08-77
		AT-A - 1953/76	15-08-77
		AT-A - 3173/77	15-08-77
		AT-B - 342565	10-04-78
		AT-B - 342570	10-04-78
		AT-B - 342575	10-04-78
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		CH-A - 634828	28-02-83
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		DK-B - 144034	23-11-81
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		ES-A5- 446187	31-10-77
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		FI-C - 62062	10-11-82
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		IL-A1- 49233	31-08-78
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		JP-A2-51138640	30-11-76
		JP-B4-60026777	25-06-85
		NL-A - 7503311	22-09-76
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		PL- P- 100615	31-10-78
		PL- P- 101884	28-02-79
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		SE-C - 425388	13-01-83
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		SU- D- 626691	30-09-78
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		DK-A - 2894/80	06-01-81
		IL-A0- 60273	16-09-80
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		DE-C0- 3473593	29-09-88
		JP-A2-59196856	08-11-84

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 90/00003

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB-A - 1582029	31-12-80	AT-A - 6054/77	15-08-79
		AT-B - 355554	10-03-80
		AT-A - 8741/78	15-08-80
		AT-B - 361457	10-03-81
		AU-B2- 521432	01-04-82
		BE-A1- 858134	16-12-77
		CA-A1- 1077506	13-05-80
		CH-A - 630344	15-06-82
		CS- P- 204008	31-03-81
		CS- P- 204009	31-03-81
		DD- C- 132433	27-09-78
		DE-A1- 2738589	02-03-78
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		DK-C - 150196	06-07-87
		ES-A5- 462346	30-05-78
		ES-A1- 462346	16-06-78
		FI-A - 772551	28-02-78
		FI-B - 68396	31-05-85
		FI-C - 68396	10-09-85
		FR-A1- 2362845	24-03-78
		FR-B1- 2362845	09-01-81
		GR-A - 63623	27-11-79
		HU- P- 177578	28-11-81
		IL-A0- 52804	31-10-77
		IL-A1- 52804	29-06-81
		JP-A2-53050131	08-05-78
		JP-B4-62016942	15-04-87
		NO-A - 772958	28-02-78
		NO-B - 144793	03-08-81
		NO-C - 144793	11-11-81
		PL- P- 106317	31-12-79
		PL- P- 107628	29-02-80